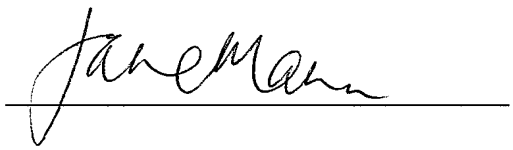
DECLARATION

I, Jane Roberta Mann, B.A.(Hons), a Translator, of Dehns, 59 St. Aldates, Oxford OX1 1ST, do solemnly and sincerely declare that I have a competent knowledge of the English and German languages and that the following is a true translation to the best of my knowledge and belief of the text of the German priority application DE 10250081.

I further declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true.

I acknowledge that wilful false statements and the like are punishable by fine or imprisonment, or both [18 U.S.C. 1001] and may jeopardize the validity of the application or any patent issuing thereon.



Signed this 16th day of June, 2011

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Water-soluble Meloxicam Granules

The present invention relates to meloxicam granules which dissolve rapidly in water, containing meloxicam, a salt forming agent which forms the meglumine, sodium, potassium or ammonium salt of meloxicam, binders, a sugar or sweetener, a carrier, optionally a flavouring and optionally other excipients, processes for preparing them and their use for treating respiratory or inflammatory complaints in mammals.

Background to the Invention

Meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide) is an active substance which belongs to the group of NSAIDs (non-steroidal-anti-inflammatory drugs). Meloxicam and the sodium and meglumine salt thereof (N-methyl-D-glucamine salt) are described in EP-A-0 002 482. EP-A-0 945 134 discloses the pH-dependent solubility characteristics of meloxicam and its salts, i.e. the sodium salt, the ammonium salt and the meglumine salt, in aqueous solution. According to this, meloxicam is an active substance which does not dissolve readily in water. The meloxicam salts, particularly the meglumine salt, exhibit improved solubility as the pH increases between 4 and 10, as shown in Table 1 of EP 0 945 134.

It is known that administering medicaments to sick animals, particularly those suffering from fever, can be done particularly simply and successfully through their drinking water. Administering to their food can also make it easier to give the medicament to the animal. It is known from EP 0945134 that meloxicam and meglumine cannot simply be compressed. The aim of the present invention is therefore to develop a granulated form of meloxicam which can be administered to the animals by mixing it into their drinking water or as a food supplement.

Description of the Invention

Surprisingly, meloxicam granules have been discovered which can easily be produced by a fluidised bed method and which, after rapidly being dissolved in

water, form a drinking water solution which is stable over at least 48 hours. It was also found that these granules can be added to the animals' food.

The invention therefore relates to water soluble granules containing meloxicam, a salt forming agent which forms the meglumine, sodium, potassium or ammonium salt of meloxicam, binders, a sugar or sweetener, a carrier, optionally a flavouring and optionally other excipients.

The meloxicam granules according to the invention have a number of advantages over existing preparations.

In sick animals an increased uptake of drinking water can be observed when a drink containing meloxicam is given. Suitable dilution of the dissolved granules allows a variable, precise dosing of the active substance meloxicam. Because of the good solubility of the meloxicam granules according to the invention in water the effects of meloxicam in the body of the sick animal set in very rapidly. The good flavour of the meloxicam granules also makes it possible to administer them as a food supplement. In addition the granules according to the invention have very good flow properties, a uniform meloxicam content, they are virtually free from dust and have a narrow particle size distribution of 125 µm to 500 µm. The total solubility of the granules in water ensures optical control of a totally dissolved active substance which is only available for therapeutic use in this form when administered in drinking water. In a preferred embodiment of the invention the salt forming agent is meglumine. In another preferred embodiment of the invention the binder may be selected from among hydroxypropyl-methylcellulose, polyvinylpyrrolidone, gelatine, starch and polyethylene glycol ether, preferably hydroxypropyl-methylcellulose, polyvinylpyrrolidone and polyethylene glycol ether, most preferably hydroxypropyl-methylcellulose and polyvinylpyrrolidone.

In another preferred embodiment of the invention the sugar or sweetener may be selected from among sodium saccharine, aspartame and Sunett®, preferably sodium saccharine or aspartame.

Particularly preferred are meloxicam granules according to the invention in which the flavouring is selected from among vanilla, honey flavouring, apple flavouring and

contramarum, preferably honey flavouring and apple flavouring. Also particularly preferred are meloxicam granules in which the carrier is selected from among lactose, glucose, mannitol, xylitol, sucrose and sorbitol, preferably glucose, lactose or sorbitol, more preferably glucose or lactose, most preferably glucose.

Particularly preferred are meloxicam granules in which the content of meloxicam is between 0.05 % and 4 %, preferably between 0.1 and 2 %, preferably between 0.3 % and 1.5 %, more preferably between 0.4 % and 1 %, most preferably 0.6 %. Also particularly preferred are meloxicam granules which contain meglumine and meloxicam in a molar ratio of about 9:8 to 12:8, preferably 10:8.

The invention further relates to processes for preparing the meloxicam granules according to the invention in which the steps a) to c) are carried out successively:

a) Preparing an aqueous granulating liquid containing binder, optionally a sugar or sweetener, meloxicam, meglumine and/or a flavouring.

b) Spraying the granulating liquid on to a carrier in a top spray fluidised bed method with a supply air current maintained at a constant temperature from 50 to 80°C, preferably 65°C.

c) Following on with a coating process with an aqueous granulating liquid by the top spray fluidised bed method containing a binder, a sugar or sweetener and/or a flavouring.

In a preferred process according to the invention the granulating liquid is prepared by stirring and heating the components to 70 to 100°C, preferably about 90°C.

A particular feature of the meloxicam granules according to the invention is that they have a long-term stability of 24 months or more when stored in their original packaging at room temperature.

A particularly preferred granulated meloxicam preparation contains meloxicam, meglumine, hydroxypropylmethylcellulose, povidone and glucose monohydrate.

The present invention further relates to the use of meloxicam granules for preparing a medicament for treating pain, inflammation, fever, acute mastitis, diarrhoea, lameness, problems of mobility and respiratory complaints in animals, preferably

acute mastitis, diarrhoea, lameness, mobility problems and respiratory complaints, preferably acute mastitis, diarrhoea, lameness, mobility problems and respiratory complaints, most preferably mobility problems or respiratory complaints. The treatment may be given in conjunction with antibiotic treatment.

The formulation according to the invention is suitable for treating animals, preferably mammals, particularly domestic pets or farm animals, such as pigs, horses, cattle, dogs or cats, preferably pigs or horses.

The meloxicam granules according to the invention are preferably used in amounts corresponding to a dosage range from 0.2 to 1.0 mg of active substance per kg of bodyweight, preferably 0.4 to 0.8 mg/kg of bodyweight, preferably 0.5 to 0.7 mg/kg of bodyweight, more preferably 0.6 mg/kg of bodyweight.

It is also preferable to use the meloxicam granules according to the invention to prepare a medicament which can be administered both in drink and also as a feed supplement.

The formulation according to the invention may contain, as the meloxicam salt, the meglumine, sodium, potassium or ammonium salt, preferably the meloxicam meglumine salt.

The proportion of meglumine is between 0.035 and 2.8 %, preferably 0.07 to 1.4%, preferably 0.21-1.05 %, more preferably 0.28-0.7 % mg/g, particularly about 0.42 % in the meloxicam granules. The possible concentrations of sodium, potassium and ammonium are calculated accordingly.

The concentration of the binders may be in the range from 20-80 mg/g, preferably 30-70 mg/g, preferably 40-60 mg/g, most preferably 50 mg/g of granules.

The concentration of the sugar may be in the range from 50-150 mg/g, preferably 75-125 mg/g, more preferably about 100 mg/g of granules.

The concentration of the sweetener may be in the range from 1-10 mg/g, preferably 2-5 mg/g, more preferably about 3 mg/g of granules.

The concentration of the carrier may be in the range from 800-985 mg/g, preferably 900-960 mg/g, more preferably about 930 mg/g of granules.

The concentration of the flavouring may be in the range from 0.1-10 mg/g, preferably 0.2-1.0 mg/g, more preferably about 0.5 mg/g of granules.

The packaging material used for the formulation according to the invention may be any of a number of standard commercial materials for granules. These include for example plastic containers, e.g. made of HPPE (High pressure polyethylene), aluminium bags or paper bags with an aluminium lining.

The meloxicam granules are produced by the top spray fluidised bed method. In this, first of all an aqueous granulating liquid solution consisting of about 50 to 70 g/kg of binder, such as PVP 25000, hydroxypropyl methyl cellulose or Macrogol 6000, preferably hydroxypropyl methyl cellulose and/or about 1 to 5 g/kg of sweeteners such as Sunett® or Na saccharine, preferably Sunett®, and/or about 0.5 to 2.5 g of flavouring, such as vanilla, honey, flavouring 203180 or contramarum, preferably honey, about 10 to 15 g of meloxicam (peg milled) and about 7 to 11 g of meglumine is produced by heating to about 70 to 100°C with stirring.

The granulating liquid is then sprayed on to a carrier such as lactose, glucose or sorbitol, preferably glucose, by a counter flow process (Top Spray). This is done, for example, using a two-component nozzle, spraying at a constant air pressure at about 50 to 80°C , preferably at about 65°C. The coating process may then be carried out using a second aqueous granulating liquid. In order to prepare a solution ready for use a stock solution should be dissolved completely in water. Then the stock solution may be adjusted to the desired concentration for use by mixing with water. To increase safety in use, the granules may have water-soluble colour markings.

The meloxicam granules according to the invention will be illustrated by the examples that follow. The skilled man will be aware that this example is intended solely as an illustration and should not be regarded as limiting.

Example 1

0.6% meloxicam granules

Recipe:	g/100 g
Meloxicam	0.6
Meglumine	0.42
Hydroxypropyl methyl cellulose	3.00
Povidone	2.00
Glucose monohydrate	93.98

Example 2

1.2% meloxicam granules

Meloxicam	1.2
Meglumine	0.84
Hydroxypropyl methyl cellulose	3.00
Collidone 25	2.0
Glucose monohydrate	92.96

Example 3

0.6% meloxicam granules

Meloxicam	0.6
Meglumine	0.42
Pharmacoat 606	4.0
Macrogol 6000	1.0
Acesulfame K	0.3
Lactose	93.68

Example 4

0.6% meloxicam granules

Meloxicam	0.6
Meglumine	0.42
Pharmacoat 606	4.75
Macrogol 6000	0.25
Acesulfame K	0.3
Liquid vanilla flavouring	0.05
Lactose	93.63

Bright yellow free-flowing meloxicam granules corresponding to Examples 1 to 4 may be prepared as follows:

The granules were stored for 3 months at 25°C at a relative humidity of 60 %. No significant changes were observed in terms of the active substance content, the water content (by the Karl-Fischer method), the visual solubility characteristics, the pH in demineralised water and the visual wettability. In order to determine the visual solubility characteristics, 5 g of the granules were dissolved in 100 ml of demineralised water at ambient temperature. After about 1 min a clear yellowish solution was obtained.

Patent Claims

1. Water-soluble granules containing meloxicam, binders, a sugar or sweetener, a carrier, a salt forming agent which forms the meglumine, sodium, potassium or ammonium salt of meloxicam, optionally a flavouring and optionally other excipients.

2. Meloxicam granules according to claim 1, characterised in that the salt forming agent is meglumine.

3. Meloxicam granules according to claim 1 or 2, characterised in that the binder is selected from among hydroxypropyl methyl cellulose, polyvinylpyrrolidone, gelatine, starch and polyethylene glycol ether.

4. Meloxicam granules according to one of claims 1 to 3 , characterised in that the sugar or sweetener is selected from among sodium saccharine, aspartame and Sunett®.

5. Meloxicam granules according to one of claims 1 to 4 , characterised in that the flavouring is selected from among vanilla, honey flavouring, apple flavouring and contramarum.

6. Meloxicam granules according to one of claims 1 to 5 , characterised in that the carrier is selected from among lactose, glucose, mannitol, xylitol, sucrose and sorbitol.

7. Meloxicam granules according to one of claims 1 to 6 , characterised in that the proportion of meloxicam is between 0.05 % and 4 %.

8. Granules according to one of claims 1 to 7, characterised in that they contain meglumine and meloxicam in a molar ratio of 9:8 to 12:8.

9. Granules according to one of claims 1 to 8, characterised in that they contain meglumine and meloxicam in a molar ratio of 10:8.

10. Process for preparing the granules according to one of claims 1 to 9, characterised in that the following steps a) to c) are carried out:

a) Preparing an aqueous granulating liquid containing a binder, a sugar or sweetener, meloxicam, meglumine and/or a flavouring.
b) Spraying the granulating liquid on to a carrier in a top spray fluidised bed method with a supply air current maintained at a constant temperature of 50 to 80°C.
c) Following on with a coating process with an aqueous granulating liquid by the top spray fluidised bed method containing a binder, a sugar or sweetener and/or a flavouring.

11. Process according to claim 10, characterised in that the granulating liquid is prepared by stirring and heating the components to 70 to 100°C .

12. Granules according to one of claims 1- 9, characterised in that they have a long term stability of 24 months or longer when stored at ambient temperature in their original packaging.

13. Granules according to one of claims 1 - 9 or 12, containing meloxicam, meglumine, a meloxicam, meglumine, hydroxypropylmethylcellulose, povidone and glucose monohydrate.

14. Use of meloxicam granules according to one of claims 1 to 9 or 12 for preparing a medicament for the treatment of pain, inflammation, fever and respiratory complaints in animals.

15. Use of meloxicam granules according to claim 13, which corresponds to a dosage range of from 0.2 to 1.0 mg of active substance per kg of bodyweight.

16. Use of meloxicam granules according to claim 12 or 13 for preparing a medicament which can be administered both in drink and as a feed supplement.

Abstract

The present invention relates to meloxicam granules which dissolve rapidly in water, containing meloxicam, a salt forming agent which forms the meglumine, sodium, potassium or ammonium salt of meloxicam, a binder, a sugar or sweetener, a carrier, optionally a flavouring and optionally other excipients, processes for preparing them and their use for treating respiratory or inflammatory complaints in mammals.